Guidance for Industry and/or for FDA Reviewers/Staff and/or Compliance

Guidance for Prescription Use Drugs of Abuse Assays Premarket Notifications

Draft Guidance – Not for Implementation

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This document supersedes the document Review Criteria for Assessment of In Vitro Diagnostic Devices for Drugs of Abuse Assays Using Various Methodologies, August 31, 1995

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Clinical Chemistry and Toxicology Branch
Division of Clinical Laboratory Devices
Office of Device Evaluation

Preface

Public Comment

For 90 days following the date of publication in the Federal Register of the notice announcing the availability of this guidance, comments and suggestions regarding this document should be submitted to the Docket No. assigned to that notice, Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852.

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Guidance for Prescription Use Drugs of Abuse Assays Premarket Notifications

This document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

I. Introduction

A. PURPOSE

This document provides FDA's guidance for premarket notification submissions and labeling for prescription use drugs of abuse in vitro diagnostic (IVD) devices. These recommendations are based on 1) current science; 2) clinical experience; 3) Food and Drug Administration (FDA) review experience; and 4) changes resulting from reengineering FDA's device review process as well as the FDA Modernization Act of 1997 (FDAMA). As advances are made in science and technology, and as additional changes resulting from implementation of legislation occur, this guidance will be re-evaluated and revised as appropriate.

This document is an adjunct to the CFR and to FDA Publication Number 97-4224, the manual entitled In Vitro Diagnostic Devices: Guidance for the Preparation of 510(k) Submissions. It is not to supersede those publications, but is to provide additional guidance and clarification concerning information that should be provided so that FDA can clear a device for marketing.

The submission should provide evidence that the device is substantially equivalent to a predicate device legally marketed in the United States. The performance of a new device should also be established by comparison of the device to a reference method, where available. NCCLS is a good source for definitive methods, reference methods, designated comparative methods, and well-characterized comparative methods.

This document provides guidance for the preparation of a submission to support a claim for prescription use. There are additional considerations if the device is intended for over the counter (OTC) use. Draft guidance for preparation of a submission for over the counter drugs of abuse devices may be found in the document, Over the Counter (OTC) Screening Tests for Drugs of Abuse: Draft Guidance for Premarket Notifications.

B. DEVICE DEFINITION

The devices discussed in this document are assays intended for the qualitative and semi-quantitative measurement of drugs of abuse in human matrices. The devices are for prescription use.

There are two primary types of analytical methods for assaying drugs of abuse. The first type is the screening test, intended to identify presumptive positive samples. The second is confirmation testing, a more definitive and accurate method of determining the presence of drug, e.g., Gas Chromatography/Mass Spectrometry (GC/MS). This document focuses on studies to characterize urine screening tests for the analytes listed below.

Amphetamine/methamphetamine
Cocaine
Opiates
Cannabinoids
Phencyclidine

This guidance may also be useful for submissions for other widely abused drugs such as barbiturates, benzodiazepines, or ethanol. Additionally, drugs may be found in matrices other than urine. This document also provides the outline for studies to support premarket applications for drugs in alternate matrices, although additional considerations, such as sample collection, environmental contamination, or sample pretreatment steps may also need to be addressed in the submission. Sponsors are urged to consult with the Division of Clinical Laboratory Devices (DCLD) before beginning studies involving new technologies or matrices.

The device panel, review method, regulations, and product codes for the assays addressed in this guidance document are listed below.

PANEL: Toxicology (91)

REVIEW REQUIRED: Premarket Notification [510(k)]

REGULATIONS: All of the test systems below are Class II.

21 CFR 862.3100 Amphetamine Test System
Identification. An amphetamine test system is a device intended to measure amphetamine, a central nervous system stimulating drug, in plasma and urine. Measurements obtained by this device are used in the diagnosis and treatment of amphetamine use or overdose and in monitoring levels of amphetamine to ensure appropriate therapy.

Product Codes:

DJL Free Radical Assay, Amphetamine

DOD Gas Chromatography, Amphetamine

DNI Liquid Chromatography, Amphetamine

DJP Radioimmunoassay, Amphetamine

DPJ Radioimmunoassay, Amphetamine (125-I), Goat Antibody, Ammonium Sulfate Sep.

DIT Thin Layer Chromatography, Amphetamine

21 CFR 862.3250 Cocaine and Cocaine Metabolite Test System
Identification. A cocaine and cocaine metabolite test system is a device intended to measure cocaine and a cocaine metabolite (benzoylecgonine) in serum, plasma, and urine. Measurements obtained by this device are used in the diagnosis and treatment of cocaine use or overdose.

Product Codes:

JXO Enzyme Immunoassay, Cocaine

DIO Enzyme Immunoassay, Cocaine And Cocaine Metabolites

DIR Free Radical Assay, Cocaine

DNG Free Radical, Benzoylecgnonine

DIN Gas Chromatography, Cocaine

DLN Hemagglutination, Cocaine Metabolites (Benzoylecgnonine)

DLN Hemagglutination, Cocaine (Syn)

LAC High Pressure Liquid Chromatography, Cocaine And Cocaine Metabolites

KLN Radioimmunoassay, Cocaine Metabolite

DOM Thin Layer Chromatography, Benzoylecgnonine

DMN Thin Layer Chromatography, Cocaine

21 CFR 862.3610 Methamphetamine Test System
Identification. A methamphetamine test system is a device intended to measure methamphetamine, a central nervous system stimulating drug, in serum, plasma, and urine. Measurements obtained by this device are used in the diagnosis and treatment of methamphetamine use or overdose.

Product Codes:

LAF Gas Chromatography, Methamphetamine

LAG High Pressure Liquid Chromatography, Methamphetamine

DJC Thin Layer Chromatography, Metamphetamine

21 CFR 862.3650 Opiate Test System
Identification. An opiate test system is a device intended to measure any of the addictive narcotic pain-relieving opiate drugs in blood, serum, urine, gastric contents, and saliva. An opiate is any natural or synthetic drug that has morphine-like pharmacological actions. The opiates include drugs such as morphine, morphine glucuronide, heroin, codeine, nalorphine, and meperidine. Measurements obtained by this device are used in the diagnosis and treatment of opiate use or overdose and in monitoring the levels of opiate administration to ensure appropriate therapy.

Product Codes:

DJG Enzyme Immunoassay, Opiate

DKT Free Radical Assay, Opiates

DJF Gas Chromatography, Opiates

DLT Hemagglutination, Opiates

LAH High Pressure Liquid Chromatography, Opiates

LAI Thin Layer Chromatography, Opiates

21 CFR 862.3870 Cannabinoid Test System
Identification. A cannabinoid test system is a device intended to measure any of the cannabinoids, hallucinogenic compounds endogenous to marihuana, in serum, plasma, saliva, and urine. Cannabinoid compounds include, among others, delta-9-tetrahydrocannabinol, cannabidiol, cannabinol, and cannabichromene. Measurements obtained by this device are used in the diagnosis and treatment of cannabinoid use or abuse and in monitoring levels of cannabinoids during clinical investigational use.

Product Codes:

DKZ Reagents, Test, Tetrahydrocannabinol

LDJ Enzyme Immunoassay, Cannabinoids

LAT Radioimmunoassay, Cannabinoid(S)

DKE Reagents, Test, Tetrahydrocannabinol

Phencyclidine Test System: Not currently classified

Product Codes:

LCM Enzyme Immunoassay, Phencyclidine

LCL Radioimmunoassay, Phencyclidine

LCK Thin Layer Chromatography, Phencyclidine

II. BACKGROUND

The prevalence and use of many drugs of abuse in the general population continue to increase. Recreational use and abuse of these drugs has led to an increased awareness of their effect on society. This concern in turn has led to an increased interest in detection methods.

Drugs are used and abused, including both legal and illegal drugs. Drug testing is most commonly focused on the urinary detection of illicit drugs (especially marijuana, cocaine, amphetamine/methamphetamine, opiates, and phencyclidine.) Profile choices and recommended cutoff levels for these drugs are based on epidemiological information available from several sources, including the Drug Abuse Warning Network conducted by the Substance Abuse and Mental Health Services Administration (SAMHSA).

III. DEVICE DESCRIPTION

A. SCREENING AND CONFIRMATION TESTING

Screening or initial testing procedures provide an initial presumptive result based on a selected cutoff concentration of a drug. Results are intended to separate presumptive positives from true negatives. Because the positive test is presumptive, it should not be reported out as a positive result without confirmation.

The most common methods used for screening are:

- enzyme immunoassay (EIA)
- radioimmunoassay (RIA)
- fluorescence polarization immunoassay (FPIA)
- thin layer chromatography (TLC)
- latex agglutination inhibition (LAI)
- enzyme multiplied immunoassay technology (EMIT)

Confirmation testing provides a more specific analysis of the targeted drug. The chemical principle of the confirmation method should differ from that used in the screening procedure. Methods used in the confirmation of presumptive positive results include:

- gas liquid chromatography (GLC)
- high performance liquid chromatography (HPLC)
- gas chromatography/mass spectroscopy (GC/MS)

B. SPECIMEN COLLECTION DEVICES

There are a variety of specimens suitable for drugs of abuse testing. The type of specimen selected for analysis may be affected by concerns about specimen collection, transport, handling, and assurance of sample integrity. Submissions for both old and new matrix types should include a specimen collection protocol and labeling instructions to assure specimen identity and integrity between the collection site and point of analysis.

Collection devices should be durable, leak-proof (when appropriate), and constructed of non-absorbing materials. The choice of a particular collection device, labeling, and the studies to demonstrate the device works may depend on the location of the collection site. Sponsors should provide information on proper collection and processing of samples and, when appropriate, on potential environmental contaminants or interferents, sample stability, potential impacts of delayed or extended transit times (between the collection site and point of analysis), and any applicable postal or mail carrier requirements. Mechanisms to ensure proper collection and possible rejection of unsuitable samples should be considered in applications.

The following are possible sample acceptance criteria (using urine as an example):

- urinary pH (4.5-8.5)
- specific gravity (1.002-1.040g/mL)
- odor
- color
- temperature (90-100°F or 32-38°C)

FDA suggests data supporting acceptance/rejection of samples be included in each premarket submission.

IV. PERFORMANCE CHARACTERISTICS

A. OVERVIEW

FDA recommendations for premarket data depend on

- the test analyte,
- the intended use, and
- whether the test is semi-quantitative or qualitative.

If multiple matrices are being used in a particular test (e.g., both serum and plasma), adequate data should be provided to support equivalent performance. Analytical studies may suffice, if no statistically significant analytical differences are noted. Clinical studies may be required if matrices do demonstrate differences in analytical performance.

Performance testing should reflect the site in which the device is intended for use. Performance for devices intended to be used in central testing laboratories may be established using trained laboratory users under environmentally controlled settings. Performance for devices intended to be used outside central testing laboratories (point of care settings) should be established at multiple representative sites by individuals who are not medical technologists or technicians.

Each data set should be accompanied by a description of the study design. This should include

- number of samples in the study
- concentrations of specimens
- method used to determine that concentration
- number of replicates
- number of days over which the analysis occurred
- number of operators involved in the study;
- description of the testing facility(ies),
- qualifications of the individuals performing the test.

In addition, you should provide information on the sample type to indicate

- unaltered clinical samples
- clinical samples diluted with known negative human urine
- control material
- prepared specimens

In particular, submissions should clearly describe what matrices were studied, what compounds were added to the matrices, and whether actual clinical samples were used. For

example, "Benzoyleconine was added to a human urine known to be drug free to a targeted concentration of 250 ng/mL. The concentration was then verified by GC/MS to be within % of the targeted concentration."

By careful design of experiments, it may be possible for performance studies to be combined (e.g., detection limits, cutoff validation, and precision studies may be established from the same or overlapping data sets.)

B. DEVICE PERFORMANCE CHARACTERISTICS

The following performance characteristics should be described in detail within the submission and summarized in the labeling:

1. Analytical sensitivity or minimum detection limit
2. Cutoff concentration
3. Specificity and Cross Reactivity
4. Interference
5. Precision
6. Method Comparison

1. Analytical Sensitivity or Minimum Detection Limit

Definition: When referring to devices capable of generating a quantitative readout, analytical sensitivity may be defined as the smallest concentration of a drug or drug metabolite that produces a response distinguishable from the background or blank value. Alternatively, this may be defined as the minimum concentration of a drug or drug metabolite that is capable of generating a positive result.

Content: The submission should contain information and data that describe the method(s) used to determine either analytical sensitivity or minimum detection limit and the value(s) established.

Study Design: Sensitivity for an assay with a quantitative readout may be established by analyzing 20 repeat determinations of the zero calibrator, calculating the mean, and adding 2 standard deviations. The detection limit for a qualitative visually read assay may be estimated by serially diluting a sample with a known amount of drug until the sample no longer renders a positive result. FDA recommends diluting in increments of 25% of the cutoff concentration for the assay. The lowest concentration of drug detected above the detection cutoff would be the detection limit. To reduce the impact of assay imprecision on analysis, we suggest that multiple aliquots at each level be evaluated. Sample concentrations should be verified using GC/MS or equivalent analytical techniques. (Note: the sensitivity for

visually read devices may be characterized in the cutoff validation studies, discussed in the next section of this document.)

Labeling: Describe the method used and the value or concentration obtained.

2. Cutoff Concentration

Definition: The cutoff concentration of an assay is the specific concentration of drug or drug metabolite in the sample that is chosen as a limit to distinguish a presumptive positive from a negative test result. Samples with concentrations above the cutoff level are considered presumptive positive and results below are considered negative.

Content: The submission should identify the cutoff of the assay. The Substance and Abuse Mental Health Services Administration (SAMHSA) has recommended threshold cutoff concentrations for 5 classes of drugs of abuse in urine:

- amphetamines/ methamphetamines
- cocaine
- opiates
- cannabinoids
- phencyclidine

In order to be consistent, FDA supports the uniform use of SAMHSA cutoff levels. These are shown in Table 1.

Table 1 SAMHSA Initial Screen Drug Cutoffs (ng/mL) In Urine

Drug	Cutoff (ng/mL)
Cannabinoids metabolites	50
Cocaine metabolites	300
Opiates: morphine, codeine	2,000
Amphetamines: amphetamine, methamphetamine	1,000
Phencyclidine	25

Submissions should include an estimate of performance (accuracy and precision) around the cutoff level. The cutoff concentration may be validated by testing a statistically valid number of spiked samples with known drug concentrations equally distributed around the cutoff. The College of American Pathologists recommends the concentration of such specimens be at 25% above and below the cutoff. For complete characterization of device performance, the concentrations of samples should be extended to drug levels that read with 100% agreement to a reference method such as GC/MS.

Study Design: An appropriate design would be to prepare and analyze 10 samples at each of the following concentrations: 25% below the cutoff, at the cutoff, at 25% above the cutoff and at serial higher and lower levels (in increments of 25%) to allow identification of the points of perfect agreement between the device being evaluated and a reference method. Samples used in these studies should be randomized and masked from the study participants to avoid reading bias.

Labeling: Provide a summary of the study design, including identification of the materials evaluated. Display results in a chart or table indicating numbers, concentrations of samples evaluated, and the positive and negative results obtained at each concentration.

Special Notes

- The rationale for selection of a particular cutoff when no SAMHSA cutoff is available should be described. Support for cutoff selection may be based on sponsor studies and/or the scientific literature. The rationale should include consideration of the clinical significance of the cutoff selected and the potential cross-reactivity of biologically active metabolites.

- For new matrices, the manufacturer should demonstrate the clinical validity of the chosen cutoff with clinical studies and/or using scientific literature. The study should evaluate a statistically significant number of samples taken from multiple individuals known to have taken the drug or who have reported that they have taken the drug in amounts consistent with typical use.

- FDA does not suggest that individuals be deliberately exposed to drugs of abuse to obtain samples for studies to validate the performance of a test. Samples may be obtained from laboratories that perform this testing or from known drug users.

- Results from visually read qualitative testing devices are dependent on the reader and on lot-to-lot production. FDA recommends that studies of test performance evaluate both the impact of readers and lots by testing cutoffs using a minimum of three users and lots. This analysis is most easily performed as part of studies to characterize device precision and/or cutoff. Observed variability should be described in device labeling.

- In all cases, cutoff concentrations should be clinically as well as analytically valid. Cutoff levels should be far enough away from the detection limit of the test to permit accurate and reproducible results. Reliable reference methods and/or clinical studies should be conducted to validate cutoff levels for new matrices or technologies.

3. Specificity and Cross Reactivity

Definition: Analytical specificity is a measure of the ability of the method to determine exclusively the drug and/or drug metabolites that are claimed to be detected without cross-reacting with other related substances that are not intended to be detected.

Content: FDA recommends that analytical specificity studies be conducted on all drugs and drug metabolites within the same class of drugs that have similar molecular structures and are likely to cross-react. The submission should contain studies that characterize cross-reactive potential for all relevant molecular entities. Information on cross-reactivity should be clearly described in device labeling.

Study Design: All drug compounds, if available, that may react with the assay should be added to drug-free urine and tested. Concentrations for testing should parallel expected levels to be found in subjects. If a compound provides positive results, it should be diluted until negative results are observed and the minimum level of cross reactive potential reported in labeling.

Labeling: Summarize the study design. An optimal way to present data is in table or chart form, listing the compound against which the device is calibrated and the lowest concentration of each cross reactive compound found to interfere with results. Concentrations should be listed in the same units, e.g., ng/mL.

4. Interference

Definition: The term interference describes the effect that a compound (or group of compounds) has on the accuracy of test measurement.

Content: The submission should contain studies that evaluate possible interference with the test by exogenous and endogenous compounds known or suspected to react with the drug.

Appropriate testing should include commonly prescribed prescription drugs and common OTC remedies such as

- acetaminophen
- acetylsalicylic acid
- caffeine
- ibuprofen

In each case, a minimum concentration of 100 µg/mL of drug should be initially examined.

In addition, appropriate alterations in matrix should be considered and evaluated. For urine, for example, the potential effects of pH, protein content, ascorbic acid content, and specific gravity level should be studied. To assist in this process, NCCLS has published a document that describes how to conduct interference testing. In addition, a listing of drugs and how they interfere with many tests is also available (Young, D.S. Effects of drugs on clinical laboratory tests. 4th Ed. Washington, DC, AACC Press, 1995.)

Note: Interferences can provide both false positive and false negative results. Both should be studied.

Study Design: Clinically relevant concentrations of each potential interferant may be added to two pools of specimen: one with the lowest concentration of the targeted drug known to consistently render positive results, and the other with the highest concentration of targeted drug known to consistently render negative results. Interfering effects, if observed, should be evaluated by diluting the interferant with a drug-free diluent until the effect is not seen.

Labeling: Present a summary of the study design. Results of evaluation with all compounds studied may be presented in tabular or chart form.

5. Precision

Definition: Precision may be defined as the ability of a test to produce the same value during repeated measurements.

Content: The submission should contain a study that evaluates precision or random error associated with use of the device. The appropriate study varies according to the type of device measurement (qualitatiave, semi-quantiative, visually read, automated assay, etc.) Spiked samples or control material is recommended for the study of precision.

Note: Stripped matrices (such as charcoal-filtered urine, etc.) are **not** considered an appropriate matrix.

FDA recommends that study materials challenge the cutoff by using levels described above under section 2. Cutoff concentration.

Manufacturers are encouraged to expand the study described in 2. Cutoff concentration to more comprehensively evaluate performance under varying concentrations.

NCCLS EP5-T2 recommends an analysis-of-variance experiment for estimating imprecision. Samples may be tested two times in the same assays twice a day fro 20 days (generating a total of 80 replicates.) This permits separate estimation of between-day, between-assay, and within-day standard deviations (SD), as well as within-run and total SDs. Acceptable alternatives that include only one run per day are also discussed in this document.

Study Design: For semi-quantitative or automated tests capable of generating a quantitative measurement, we suggest using the above described NCCLS format and descriptive results of means and coefficients of variation.

For visually read tests, the random error of visual interpretation should be characterized by at least 3 operators. Multiple lots of the device should be studied. One suggested design is to have each operator evaluate 10 samples for each level of study material over a minimum of 2 to 3 days. Descriptions of masking, randomization of samples, and any other efforts undertaken to minimize study bias should be described in the submission.

In order to demonstrate precision across the range of semi-quantitative assay, you should present replicate measurements of calibrators.

Studies should be performed in settings reflecting planned use. For devices to be marketed to centralized laboratories, studies may be performed by experienced laboratory users with controlled operating environments. For devices to be marketed to point of care settings, studies should be performed by personnel without training as medical technologists or technicians at a minimum of three representative point of care sites. Data should be presented according to site and operator. Information on educational background of the operators should be included. During point of care studies, the written and verbal information available to operators should parallel that expected under usual conditions of use.

Labeling for Semi-quantitative or Automated Tests: Labeling should include a description of the study design and results with confidence intervals. Information should include:

- concentration of the study samples
- number of runs per day
- number of days of the study
- means
- standard deviations
- coefficients of variation

Labeling for Visually-Read Tests: Labeling should include a description of the study design and results. Information should include:

- concentration of the study samples
- the number of samples
- the number of operators
- the number of testing days

A summary of the test results recorded by each operator may be included in a table or chart according to the concentrations tested. Operator data may be pooled it there is no significant inter-operator differences observed.

Labeling for Semi-Quantitative Tests: Labeling should include a table summarizing the precision data from replicate testing of calibrators.

Labeling for Point of Care Tests: For tests with a point of care claim, the summary of study design should include:

- sites
- operators
- samples
- testing days

Data should be presented by site or operator unless no significant differences are observed.

6. Method Comparison

Definition: Comparative performance of a new assay can be established by comparison of the device to a predicate device legally marketed with the U.S. Comparison may be by device to device correlation or by evaluating data of the new device against an accepted reference method, e.g., GC/MS, and evaluating performance determined in this manner in comparison to a previously marketed test.

FDA strongly recommends that all or part of comparative studies (especially studies of cutoff levels) be performed against reference testing methodologies. Comparisons between varying immunoassays often provide limited information on device performance because of variable reactivity of these assays to clinically active and significant forms of drug compounds.

Content: Ideally a statistically significant number of positive and negative clinical samples known to be free from interfering substances and other drugs should be used in device studies. Forty positive and negative samples are generally considered a minimum sample size for a well-established matrix. Comparisons are best when performance is characterized in relation to a reference method.

Drug concentrations in the sample should cover the entire range of possible test results, with particular emphasis on values near the cutoff concentration. FDA strongly recommends that a minimum of 10% of samples be distributed between the cutoff concentration and a value 25% above the cutoff and a minimum of 10% of samples be distributed between the cutoff and a value 25% below the cutoff. These concentrations should be determined by GC/MS and all forms or metabolites of the drug that SAMHSA recommends for including in confirmation testing should be evaluated. In the absence of SAMHSA recommendation, all drugs or metabolites known to significantly cross-react should be studied.

All positive results and a minimum of 10% of negative results should be analyzed by a reference method. For new matrices or novel technologies, FDA recommends that all results be analyzed by a reference method.

We strongly encourage use of clinical samples whenever possible. Reference laboratories may be utilized to ensure that clinical samples selected span the appropriate range for testing and adequately challenge the cutoff point.

Two examples of contingency tables to present study data are as follows:

New device	Negative by GC/MS or Predicate	Near Cutoff Negative (between -25% and cutoff)	Near Cutoff Positive (between cutoff and +25%)	GC/MS Positive (greater than +25%)	Percent Agreement with GC/MS
Positive					
Negative					

		Predicate Device	
		+	-
New Device	+		
	-		

When the results of a new device are compared to a predicate device without confirmation by reference testing, only percent agreement is known.

In addition to tables similar to those above, you should provide the raw data from the study. We recommend presenting this information in a table showing the results from the new assay and the predicate assay, for each of the clinically significant drugs or metabolites, as well as all GC/MS results.

If comparisons to the predicate are performed rather than comparisons to a reference method, it is recommended that all discrepant data points be investigated further using a reference method.

If clinical investigators are involved in the study, then it may be necessary to submit a Financial Disclosure Statement. For the final rule on Financial Disclosure Statements, please refer to the Federal Register, February 2, 1998 (63 FR 5233).

Study Design: For matrices or technologies that have been well-characterized, you should obtain at least 80 clinical samples from a reference laboratory. All positive and a portion of negative results should be characterized by GC/MS. Drug concentrations in the samples should cover the range of possible results with particular attention to the cutoff point. We strongly suggest that a minimum of 10% of the total number of samples fall between the cutoff and a concentration 25% above the cutoff and another 10% of the total number of samples between the cutoff and a concentration 25% below the cutoff. These concentrations should be determined by a reference methodology and when available represent confirmation testing results according to SAMHSA guidelines. If SAMHSA has no guidelines, drugs or metabolites known to cross react with the drug being measured should be evaluated or considered in the study design.

Labeling: Provide a summary of the study design with:

- sample type
- instrument used, if applicable
- number of runs or number of testing days

Contingency testing showing results of the new device compared to a reference method and any comparisons to the predicate device should be included in labeling.

For point of care devices, a summary of the study design should include information on sites and operators, if appropriate. Data may be pooled if statistically acceptable.

If discrepancy testing has been performed, GC/MS values for all metabolites found in discordant samples should be presented.

V. ADDITIONAL INFORMATION

A. STABILITY STUDIES

Stability refers to the ability of a product to resist conditions, temperature, humidity and length of storage, which may affect the product's performance. Files should be maintained at the manufacturing site in accordance with applicable Good Manufacturing Practices (GMPs) and Quality Systems Regulations (QSRs).

B. SPECIMEN COLLECTION, HANDLING, AND STORAGE

Information supporting the recommended sample collection, handling, and storage conditions should be presented in the submission. This information may be omitted if the recommendations are standard for the industry, but should be provided when the matrix or technology is not well characterized. Literature references may be used if they are adequately linked to the specific device being considered.

C. CLINICAL INVESTIGATIONS

In certain instances it may be necessary to collect clinical data to establish substantial equivalence of a new device to a predicate device. Examples include a new methodology or technology, a new or uncharacterized matrix, or when a new cutoff is being employed. Sponsors are urged to consult with the Division of Clinical Laboratory Devices before proceeding with these studies.

VI. ADDITIONAL LABELING CONSIDERATIONS

The manufacturer should assure that labeling complies with Section 502(a) of the Federal Food Drug and Cosmetic Act (the Act) in that the Directions for Use are adequate, and are not false or misleading. According to 21 CFR 801.119, all in vitro diagnostic devices shall be deemed to be in compliance with the requirements of 502(a) and 502(f)(1) of the Act if they meet the requirements of 21 CFR 809.10, labeling for in vitro diagnostic products. The phrase "For In Vitro Diagnostic Use" should also appear in the labeling. List the name and place of the manufacturer, packer, or distributor. State the date of last labeling revision.

All abbreviations and acronyms used in the labeling should be clear and well-defined. The following suggested labeling formats are intended to supplement CFR 809.10, and to bring about uniformity and clarity in the critical information presented to the user.

A. INTENDED USE

The following information should be stated in the intended use:

- prescription, point of care, or OTC
- qualitative or semi-quantitative
- the targeted drug/metabolite
- the cutoff concentration
- any special instrument requirements
- the type of specimen

A sample intended use statement is given below.

> *ABC's cannabinoid test is a prescription assay intended for use in drug rehabilitation clinics and physician offices. It provides qualitative screening results for cannabinoids (THC) in human urine at a cutoff concentration of 50 ng/mL. For In vitro Diagnostic Use.*

The following statement in bold print should immediately follow the Intended Use statement:

> **This assay provides only a preliminary result. Clinical consideration and professional judgment must be applied to any drug of abuse test result, particularly in evaluating a preliminary positive result. In order to obtain a confirmed analytical result, a more specific alternate chemical method is needed. Gas Chromatography/Mass Spectroscopy (GC/MS) is the preferred confirmation method.**

We have observed wide variability in performance around the claimed cutoff, particularly with visually read tests. The reason for this variable performance among assays may be due to the fact that a) many manufacturers desire to use SAMHSA recommended cutoffs even thought their assay's results are not consistent with that cutoff, and b) it is sometimes difficult to manufacture visually read devices that perform in a manner that is consistent with SAMHSA cutoffs. Users, however, expect that a device reasonably distinguishes samples that have drug concentrations above and below the claimed cutoff of the assay.

Because variable performance around the cutoff may result in a false positive or false negative test result, it is important for users to be alerted when devices do not perform in a manner which is consistent with the claimed cutoff. For this reason, manufacturers are urged to include the following statement when their assay, at concentrations 50% above or below the claimed cutoff concentration, provides more incorrect results than correct results:

> *It should be noted that although the cutoff of this assay is identified as xxx ng/mL, a significant number of samples below and/or above this cutoff may render incorrect results. Please refer to the performance section of this package insert.*

B. SUMMARY AND EXPLANATION OF THE TEST

A general description of the drug, including pharmacokinetic information, is helpful. Clearance rates for the drug may also be included. Examples are presented in Table 3.

Table 3. Clearance Rate Examples

Drug	Drug Use Within	After Drug Use For
Pot/Marijuana (Cannabinoids)	1 to 3 hours	1 to 7 days
Crack (Cocaine)	2 to 6 hours	48 to 72 hours
Heroin (Opiates)	2 to 6 hours	24 to 72 hours
Speed/Uppers (Amphetamine/methamphetamine)	4 to 6 hours	48 to 72 hours
Angel Dust/PCP (Phencyclidine)	4 to 6 hours	7 to 14 days

C. TEST PRINCIPLE

Provide a short description of the scientific principle of the test methodology, including the chemical reactions and techniques involved, and the chemical, physical, physiological, or biological principles of the test.

D. REAGENTS

You should provide the following information about the reagents as appropriate. You should also clearly distinguish calibration materials and quality control materials.

- quantity, proportion, or concentration of each reactive ingredient
- activity and biological source of the material
- instructions for reconstitution, mixing, or dilution
- storage instructions for unopened and opened product, and expiration times, as appropriate

E. SPECIMEN COLLECTION AND HANDLING

You should provide the following information about specimen collection and handling. Also, state the storage, handling, or shipping instructions for the protection and maintenance of specimens, and any comments concerning the stability of the specimen.

- type of specimen to be collected, e.g., whole blood, plasma, urine
- amount of specimen required
- any special precautions regarding specimen collection requirements
- any known interfering substances or conditions, e.g., using nasal inhalants, diet pills, diarrhea medicines, or ingesting poppy seeds

F. TEST PROCEDURE OR DIRECTIONS FOR USE

You should provide the following information as appropriate:

- materials provided
- materials required but not provided
- step-by-step instructions adequate for the intended setting and user
- recommendations for calibration frequency
- stability of the final reaction

G. QUALITY CONTROL

1. External Quality Control

Quality control materials included with the device or recommended for use should have target ranges that are traceable to GC/MS. SAMHSA recommends that the concentration of drug(s) in positive and negative controls be approximately 25% above and below the cutoff concentration of the assay. A statement to that effect should appear in the labeling if the controls contained in the kit do not satisfy that recommendation.

Provide recommendations for frequency of use along with the following statement in the labeling.

Users should follow the appropriate federal, state, and local guidelines concerning the running of external quality controls.

Directions for interpretation of results of quality control samples, and information concerning the satisfactory limits of performance, should also be included, where appropriate.

2. Internal Quality Control

The format of the device may include "built-in" process controls. Process controls may indicate that the sample has migrated appropriately, the correct volume of sample or reagents has been added, or that a sequence of reagents has been added in the correct order. The purpose and function of the process control should be stated in the labeling. Information should be presented that demonstrates how the control line monitors each function being claimed. Statements such as "the control line indicates that the test has worked properly" are not appropriate, unless a full hazard analysis is provided which indicates that the control monitors all aspects of the device that could go wrong.

3. Electronic Quality Control

The format of the device may be such that electronic quality checks may be appropriate. The labeling should explain the purpose and function of electronic/optic/sensor quality checks.

The labeling should indicate a recommendation for the frequency of electronic checks and directions for interpretation of the results of electronic checks.

H. RESULTS

Explain in the labeling how to interpret test results, relative to the assay cutoff concentration of drug. If the result requires a calculation, provide a sample calculation.

The assay cutoff concentration is that concentration which separates a negative result from a presumptive positive in a screening device. SAMHSA has established guidelines for Federal Workplace Drug Testing Programs that specify cutoff values, as targets for screening and confirmation assays. These current cutoff concentrations are shown in Table 2.

Table 2. SAMHSA Recommended Cutoff Concentration in ng/mL in Urine.

Test	Screen	Confirm
Marijuana metabolites	50	15
Cocaine metabolites	300	150
Opiates (morphine, codeine)	300	300
Amphetamine/Methamphetamine	1000	500
Phencyclidine	25	25

As technology and user demand increase, the cutoff values for some drugs of abuse assays may not always be in concurrence with SAMHSA recommended limits. FDA recognizes that assay cutoffs differing from those proposed by SAMHSA are sometimes used in various settings. In such instances, FDA advises that the SAMHSA recommended cutoff(s) be stated in the package insert, e.g., "The SAMHSA recommended cutoff for (this drug analyte) is (assay cutoff)."

I. LIMITATIONS

A list of substances known to interfere with the device should be presented under the Limitations section of the package insert. In addition, FDA believes the following limitation should be included in the labeling:

There is a possibility that other substances and/or factors not listed above may interfere with the test and cause false results, e.g., technical or procedural errors.

J. PERFORMANCE CHARACTERISTICS

Recommendations for representation of Performance Characteristics in the labeling are provided in section III, above. Additionally, the assay range, dynamic range of the assay, or linearity, as appropriate, should be stated in the package insert.

K. BIBLIOGRAPHY

Include a bibliography of references cited in the text, and any other references related to the subject matter.

VII. OUTSIDE BOX LABELING

In addition to in vitro labeling requirements for package inserts, the following labeling statement should be included on the outside box labeling. Note: This statement should appear on the outside box label and on all promotional material for drugs of abuse test kits.

This assay provides only a preliminary result. A more specific alternate chemical method is needed to obtain a confirmed result (see package insert).

VIII. BIBLIOGRAPHY

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National Institute on Drug Abuse (NIDA): Urine Testing for Drugs of Abuse. Res Mono 73, 1986.

Drug Testing in the Workplace. JAMA 258:504-509, 1987.

National Institute on Drug Abuse (NIDA): Technical, Scientific, and Procedural Issues of Employee Drug Testing. Consensus Report. DHHS 1988.

EP5-T2: Precision Performance of Clinical Chemistry Devices-Second Edition; Tentative Guideline (1992). NCCLS, Summer, 1995.

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Write It Right: Recommendations for Developing User Instruction Manuals for Medical Devices Used in Home Health Care. HHS Publication FDA 93-4258, 1993.

IX. GLOSSARY

Amphetamines - A term generally used to include amphetamine and methamphetamine. Other phenethylamines, not all of which are abused, may cross-react with some antibodies used in immunoassay test kits and may be included in this group.

Calibrator - A device intended for use in a test system to establish points of reference that are used in the determination of values in the measurement of substances in human specimens.

Cannabinoids - A family of compounds, some of which are psychoactive, found in the common hemp plant, or Cannabis sativa. Most of the pharmacological effects are produced by delta-9-tetrahydrocannabinol. In urine drug testing, the prior use of marijuana is established by the detection of metabolites of cannabinoids. These metabolites are generally inactive, but are often present in significant quantities. The most abundant metabolite is 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid, sometimes referred to as 9-carboxy-THC. Most immunoassays and confirmation procedures are directed toward this metabolite.

Chromatography - Any of a variety of techniques used to separate mixtures of drugs and their metabolites and other chemicals into individual components based on differences in their relative affinities for two different media, a mobile phase and a stationary phase. In gas chromatography, the mobile phase is an inert gas such as nitrogen or helium, and the stationary phase is a high-boiling liquid bound to fine particles packed in a glass column, or bound to the inner surface of a glass capillary column.

Cocaine - An alkaloid, methylbenzoylecgonine, obtained from the leaves of the coca tree (Erythroxylon sp.). It is a central nervous system stimulant that produces euphoric excitement. Abuse and dependence on cocaine constitute a major drug problem. It is used as the hydrochloride salt, as well as the free base.

Collection Site - A place designated where individuals present themselves for the purpose of providing a urine specimen to be analyzed for the presence of drugs.

Confidence Interval - is a range of values for a variable computed in a prescribed manner which assures that in repeated random sampling, 95% (for a 95% confidence interval) of the

time the intervals determined in the prescribed way will bracket (include) the unknown true population parameter.

Confirmation testing - The process of using a second analytical procedure to verify the presence of a specific drug or metabolite. The second procedure is independent of the initial test and uses a different technique and chemical principle from that of the initial test in order to ensure reliability and accuracy.

Cross Reactivity - The degree to which an antibody interacts with antigens other than the one used to produce the antibody. This is a property of nearly all naturally derived antibodies.

Cutoff - The defined concentration of an analyte in a specimen at or above which the test is called positive and below which it is call negative (see Threshold). This concentration is usually significantly greater than the sensitivity of the assay.

Documentation - A printed or written record retained as support or proof of claims made in reporting test results or in the laboratory certification process.

Drug metabolite - A modified form, or degradation product of a drug, produced by a metabolic process.

False Negative - A test result which states that no drug is present when, in fact, a tested drug or metabolite is present in an amount greater the threshold or cutoff amount.

False Positive - A test result which states that a drug or metabolite is present when, in fact, the drug or metabolite is not present, or is present in an amount less than the threshold or cutoff value.

GC/MS - An abbreviation for the instrumental technique that couples the powerful separation potential of gas chromatography (GC) with the specific characterization ability of mass spectroscopy (MS).

Initial Testing Procedures - The initial test, or screening test, is used to identify those specimens that are negative or positive for the presence of drugs or their metabolites. Negative specimens need no further examination and need not undergo a more costly confirmation test.

Limit of Detection - The minimum amount of an analyte that can be detected with confidence by a testing procedure.

Mass Spectrometry - Analysis using an analytical instrument that provides accurate information about the molecular mass and structure of complex molecules. This technique can identify and quantify extremely small amounts of drugs or metabolites by their mass-fragmented spectrum.

Matrix - The material or sample in which an analyte is measured, e.g., whole blood, serum, plasma, urine, tears, sweat, meconium, saliva.

Opiate - A term used to designate drugs derived from opium such as morphine and codeine, together with the semi-synthetic congeners such as heroin. Immunoassay kits for opiates are generally directed to detect morphine, but cross react with other opiates as well.

OTC – Over the counter, applies in this document to medical devices that can be purchased without a prescription.

Passive Inhalation - The exposure of non-smoking subjects, through inhalation, to side-stream smoke from active smokers, thereby raising the possibility that a non-user of marijuana may test positive for metabolites of delta-9-tetrahydrocannabinol.

Phencyclidine (PCP) - An animal tranquilizer, which when ingested by humans, can cause an hallucinogenic reaction, or other psychotic reactions such as extreme anxiety or panic. Hypertensive crisis and CNS seizures have also been reported.

Point of Care – for the purposes of this document, applies to testing performed outside of a laboratory environment, generally nearer to or at the site of the patient.

Prescription Use – applies in this document to medical devices that are sold on the prescription or other order of practitioners licensed by law in the state in which they reside, such as physicians and dentists. See also 21 CFR 801.109 Prescription Devices.

Predicate Device - A legally marketed medical device with the same intended use as the test being submitted for clearance by a 510(k) premarket notification. Since the Safe Medical Device Act (SMDA) of 1990, it is no longer required that the first marketing of the predicate device antedate March 28, 1976.

Screening - See Initial Testing Procedures.

Security - The process by which specimens are protected from tampering, contamination, and mix-up while maintaining confidentiality of the test results. The process should be organized in such a way that unauthorized persons do not have access to specimens and any breach of security is immediately recognizable.

THC - Delta-9-tetrahydrocannabinol, the most pharmacologically active of the cannabinoids (See Cannabinoids).

Validation - The process by which an analytical technique is proven as to its accuracy, precision, sensitivity, linearity, and selectivity.